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ORIGINAL ARTICLE

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HOXA10 expression profiling in prostate cancer

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Background: HOX genes encode transcription factors that play key roles in modulating normal tissue morphogenesis, differentiation and homeostasis. Disruption of normal HOX gene expression occurs frequently in human cancers and is associated with both tumor promoting and suppressing activities. Among these is, *HOXA10*, a pleiotropic gene that is critical for normal prostate development. In this study we characterized HOXA10 expression in human and mouse PCa to gain insights into its clinical significance.

Methods: A meta-analysis of HOXA10 mRNA expression was carried out across several publicly available data sets. Expression of HOXA10 protein expression was assessed by immunohistochemistry (IHC) using human radical prostatectomy (RP) cases. We correlated HOXA10 expression to clinicopathological features and investigated its relationship to biochemical recurrence (BCR) after RP by the Kaplan-Meier method. HOXA10 mRNA and IHC protein expression was also examined in a mouse model of *Pten*-null PCa.

Results: A meta-analysis of HOXA10 gene expression indicated dysregulated expression of HOXA10 in human PCa. IHC profiling of HOXA10 revealed inverse correlations between HOXA10 expression and Gleason pattern, Gleason score, and pathological stage ($P < 0.01$). Patients with low expression profiles of HOXA10 were associated with a higher risk of BCR, (OR, 3.54; 95%CI, 1.21-16.14; $P = 0.049$) whereas patients with high HOXA10 expression experienced longer times to BCR ($P = 0.045$). However, HOXA10 was not an independent predictor of BCR (OR, 1.52; 95%CI, 0.42-5.54; $P = 0.52$). Evaluation of expression patterns of HOXA10 in mouse prostate tumors mimicked that of humans.

Conclusions: Our findings show that HOXA10 expression is inversely associated with tumor differentiation and high HOXA10 expression is associated with improved BCR-free survival. This study provides human and mouse evidence to suggest tumor suppressive roles for HOXA10 in the context of prostate cancer.

KEYWORDS
biomarker, HOXA10, prostate cancer, radical prostatectomy

1 | INTRODUCTION

Radical prostatectomy (RP) is the primary curative treatment option for patients with localized prostate cancer (PCa). Nevertheless, recurrence after RP occurs in approximately one third of the patients.[1,2] Predicting disease recurrence remains a major challenge due to the complex nature of PCa and while postoperative factors such as Gleason score (GS) and pathological stage are useful as prognostic factors,[3] there are no molecular biomarkers that can reliably predict biochemical recurrence (BCR). Identifying factors that contribute to BCR could help clarify our understanding of prostate cancer biology and enhance our ability to identify patents that may benefit from post-surgical adjuvant therapy.

Homeobox genes are transcriptional regulators that play critical roles in controlling morphogenesis, differentiation and regional development along the anteroposterior axis during embryogenesis.[4,5] The human genome contains 39 homeobox genes, which are categorized into four families (*HOXA*, *HOXB*, *HOXC*, and *HOXD*).[6] In the developing embryo, the homeobox proteins HOXA10, HOXA13 and HOXD13 modulate morphogenesis and normal development of the prostate gland.[7] However, aberrant expression of homeobox genes is often observed in cancers and have been implicated with increased tumor growth, proliferation, angiogenesis and cell cycle.[8] *HOXA9* and *HOXB13* are the two HOX genes most commonly associated with solid tumors while overexpression of *HOXC* is observed in human prostate cancer.[9]

HOXA10 has been shown to play both tumor promoting and tumor suppressing roles in various solid cancer models.[10–13] Furthermore, a positive correlation was observed between HOXA10 expression and patient prognosis in gastric cancer, whereas, a negative correlation was reported in ovarian adenocarcinoma thus indicating that HOXA10 acts in a context-dependent manner.[14,15]

To further elucidate the clinical significance of HOXA10 in human cancer, we focused on examining the evaluating HOXA10 expression in human prostate adenocarcinoma and its associations with clinicopathological features. We further examined its temporal expression in a well-established mouse model of *Pten*-deficient PCa.[16]

2 | MATERIAL AND METHODS

2.1 | Human mRNA data

HOXA10 gene expression analysis were performed using publicly available datasets in the Oncomine cancer microarray database.[17]

2.2 | Patient population

Archival tissue blocks from a cohort of 112 radical prostatectomy (RP) cases performed between January 2006 and March 2010 at Kindai University Faculty of Medicine were selected. Patients with preoperative hormone therapy or radiotherapy were excluded. Biochemical recurrence (BCR) was determined to be PSA failure after RP. Patient details are summarized in Table 1.

TABLE 1 Summary of clinicopathological characteristics

No. of patients	112
Age	67 (53-77)
Initial PSA(ng/mL)	11.3 (3.6-53)
Gleason pattern	
3 + 3/3 + 4/3 + 5	19/32/5
4 + 3/4 + 4/4 + 5	16/10/23
5 + 3/5 + 4/5 + 5	2/4/1
Gleason score	
6	19
7	48
8-10	45
Stage	
pT2	69
pT3/pT4	42/1
Biochemical failure	
Relapse−free	45
PSA failure	67
PSA nadire of after RP	
<0.005	45
≧0.005	67

2.3 | Immunohistochemical (IHC) analysis

Tissue microarrays, consisting of prostate tumor and normal adjacent tissue, were constructed from formalin-fixed paraffin embedded tissue blocks. Selected donor blocks, originally assessed for pathological examination after surgery, were pulled and representative areas of tumor and normal adjacent tissue were marked and cored (2-5 1.5 mm cores) using a custom manual coring instrument and embedded into recipient blocks. Serial sections were cut and placed on positively charged slides. A slide was stained with hematoxylin and eosin for confirmation by a trained urologist.

For IHC studies, adjacent serial sections were subjected to antigen retrieval with DAKO Target Retrieval Solution (Agilent, Santa Clara, CA), for 20 min in a steamer, blocked in normal serum and incubated overnight at 4°C with the anti-HOXA10 (N-20, sc17158, 1:150; Santa Cruz Biotechnology Inc., Heidelberg, Germany), stained using the ABC kit (Vector Laboratories, Burlingame, CA) following manufacturer's protocols, developed in DAB (Invitrogen, Camarillo, CA) and counterstained with hematoxylin.

Stained samples were analyzed by light microscopy and scored according to intensity (4 point scale: 0 = negative; 1 = weak; 2 = moderate; and 3 = strong) and distribution (recorded as percent positive). An index score (IS) was determined by the product of intensity × distribution. The final index score represents the average value from two independent blinded scorers.

2.4 | Animal studies

All mice were housed at the Kindai University Faculty of Medicine Animal Facility in accordance with institutional guidelines. *Pten*-deficient (PSA^{Cre};$Pten^{loxP/loxP}$) have been described previously.[16] *Pten*-wildtype (PSA^{Cre};$Pten^{+/+}$) were as normal controls.

For mouse *Hoxa10* mRNA analyses, qRT-PCR was performed on prostate glands collected from wildtype and tumor bearing *Pten*-deficient mice. Briefly, total RNA was extracted and purified from prostate tissues preserved in RNALater solution using the RNeasy Mini Kit (Qiagen, Germantown, MD) following the manufacturer's instructions. cDNA was synthesized using the PrimeScript First Strand cDNA Synthesis Kit (Takara, Shiga, Japan). The sequences for the mouse *Hoxa10* primer used were forward; 5′CTGTCTCCAGCCCCTTCAGAAA3′ and reverse; 5′TCTGGTGCTTCGTGTAAGGGA3′. Relative change in gene expression was calculated using $2^{-\Delta\Delta Ct}$ method using *Gapdh* as an internal control.

IHC of HOXA10 was performed in formalin-fixed paraffin embedded tissue sections of mouse prostates collected at the indicated time and stained as previously described.

2.5 | Statistical analysis

Data were reported as mean values ± standard error unless noted. A two-tailed Student's *t*-test used for paired analysis and one-way ANOVA on ranks for multiple comparisons. Correlations between HOXA10 expression and clinicopathological features were performed using Pearson's correlation. We used receiver operating characteristics (ROC) analysis to identify the optimal cutoff value of the HOXA10 IS. Associations between high HOXA10 (IS ≥150) or low HOXA10 (IS <150) and clinicopathological features were calculated using Pearson's Chi Square test. The Kaplan-Meier method was used to estimate BCR survival curves and statistical significance was determined by the Log-rank test. Univariate and multivariate Cox regression was used to evaluate the associations between clinical covariates and BCR. Hazard ratio and 95% confidence interval were estimated from Cox proportional hazard models. For multivariable Cox regression models, variables that were statically significant ($P < 0.05$) in univariate analysis were included. Analyses were performed with StatMate V Win&Mac Hybrid Value Package for Microsoft Windows. A $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Meta-analysis of *HOXA10* gene expression in human tissues

We first performed a meta-analysis of *HOXA10* gene expression in human normal and cancer tissues using publicly available datasets from the Oncomine microarray database.[17] Overall, *HOXA10* mRNA levels were higher in normal reproductive organs including prostate, uterus and vagina (Figure 1A). In normal prostate, *HOXA10* levels had fold increases of 8.040, $P < 0.001$ and 14.730, $P < 0.001$ in normal versus normal analysis, Roth Normal and Roth Normal 2, respectively. In the Brittner multi-cancer data set, colorectal, prostate and esophageal cancer had the greatest levels of *HOXA10* overexpression, exhibiting fold changes of 3.400, $P < 0.001$; 3.133, $P < 0.001$; and 2.464, $P < 0.015$, respectively (Figure 1B). Notably, six of eight prostate cancer datasets showed decreased levels of *HOXA10* in tumor tissues versus normal prostate tissues (Figure 1C).[18–25] These findings suggest that HOXA10 is critical for normal prostate maintenance and support the notion that dysregulated expression may be associated with PCa.

3.2 | Characterization of HOXA10 expression in human prostate cancer

To determine the clinical significance of HOXA10 in human prostate cancer, we performed immunohistochemical analyses on prostate tissue microarrays consisting of normal adjacent and cancer tissue cores from 112 patients that underwent radical prostatectomy (Table 1). Representative images of HOXA10 staining in benign and prostate tumor are shown in Figure 2. Strong nuclear HOXA10 staining was predominantly observed in epithelial cells in benign prostate tissue. In PCa cases, HOXA10 staining varied in both normal adjacent tissue and dysplastic glands. Expression patterns ranged from low to high distribution with weak to moderately strong staining present in both the nucleus and cytoplasm. Notably, immunoreactivity of HOXA10 appeared to decrease in poorly differentiated tumors (Figure 2).

To further understand the clinical relevance of HOXA10 in PCa, we examined HOXA10 expression and it association to clinicopatholigal features. We used the HOXA10 IS as a semi quantitative means to measure the staining intensity and distribution of nuclear expression of HOXA10 in normal prostate and PCa. Notably, HOXA10 expression tended to be greater in cancer regions compared to adjacent normal areas (Figure 3A-B). However, the HOXA10 expression was inversely associated with histological grade and pathological stage (Table 2 and Figures 3B and 3C). A single case of metastatic PCa was available for evaluation and scored but was not included in the analysis since it was a single case. However expression in the metastatic lesion was higher than the primary, HOXA IS 180 versus 70, respectively.

3.3 | Association between HOXA10 expression and clinical features

A HOXA10 IS of 150 was determined to be the optimal cutoff value for the HOXA10 expression analysis (Figure 4). Statistically significant associations between high and low HOXA10 index scores were observed for GS and tumor differentiation (Table 3).

The significance of HOXA10 expression and the probability of biochemical recurrence after RP were further explored by Kaplan-Meier analysis. Patients with low HOXA10 expression (HOXA10 IS ≤150) experienced shorter times to biochemical recurrence compared to patients with high HOXA10 expression ($P = 0.045$; Figure 5). On univariate analysis, low HOXA10 IS revealed a marginal

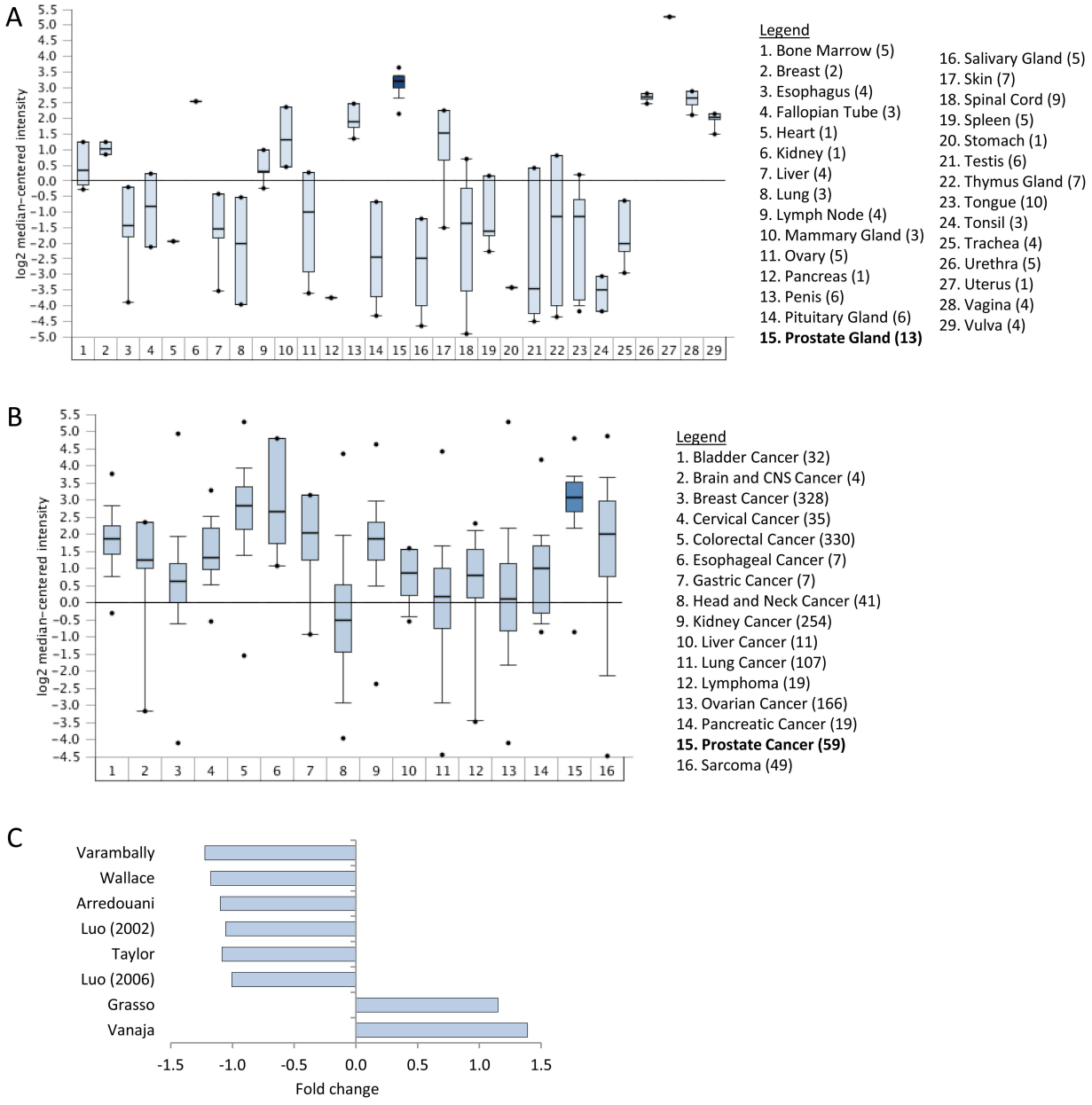

FIGURE 1 Evaluation of *HOXA10* expression in human tissues. Gene expression profiles of *HOXA10* in human normal (Roth Normal 2 data set, A) and cancer (Brittner Multi-cancer, B) tissues from data sets queried in the Oncomine database repository. (C) *HOXA10* expression in prostate cancer versus normal prostate in Oncomine public datasets. [Color figure can be viewed at wileyonlinelibrary.com]

statistically relevant association for biochemical recurrence (OR 3.54, $P = 0.049$), but was not an independent predictor (OR 1.52, $P = 0.52$, Table 4).

3.4 | Reduced HOXA10 is observed in a mouse *Pten*-null prostate cancer model

To provided further insights into the potential biological significance of HOXA10 and prostate cancer, we examined HOXA10 in a transgenic mouse model of prostate cancer that closely mimics human prostate cancer.[16] *HOXA10* mRNA levels were lower in prostate tumors from *Pten*-deficient prostates compared to those of wildtype mice ($P < 0.001$, Figure 6A). Figure 5 shows the IHC expression of HOXA10 in the spatial/temporal continuum of prostate cancer development and progression in the *Pten*-deficient prostate cancer model. As in humans, HOXA10 is strongly expressed in normal prostate, of tumor-free wildtype mice. HOXA10 was still present in low-grade intraepithelial neoplasia (LG-PIN) lesions but was notably absent in the basal cells of mouse high-grade PIN (HG-PIN) and moderately differentiated cancer glands, and was mostly lacking in advanced poorly differentiated tumors. Together, our findings show that HOXA10 is decreased in poorly differentiated PCa and suggest important functional roles for HOXA10 in tumor differentiation.

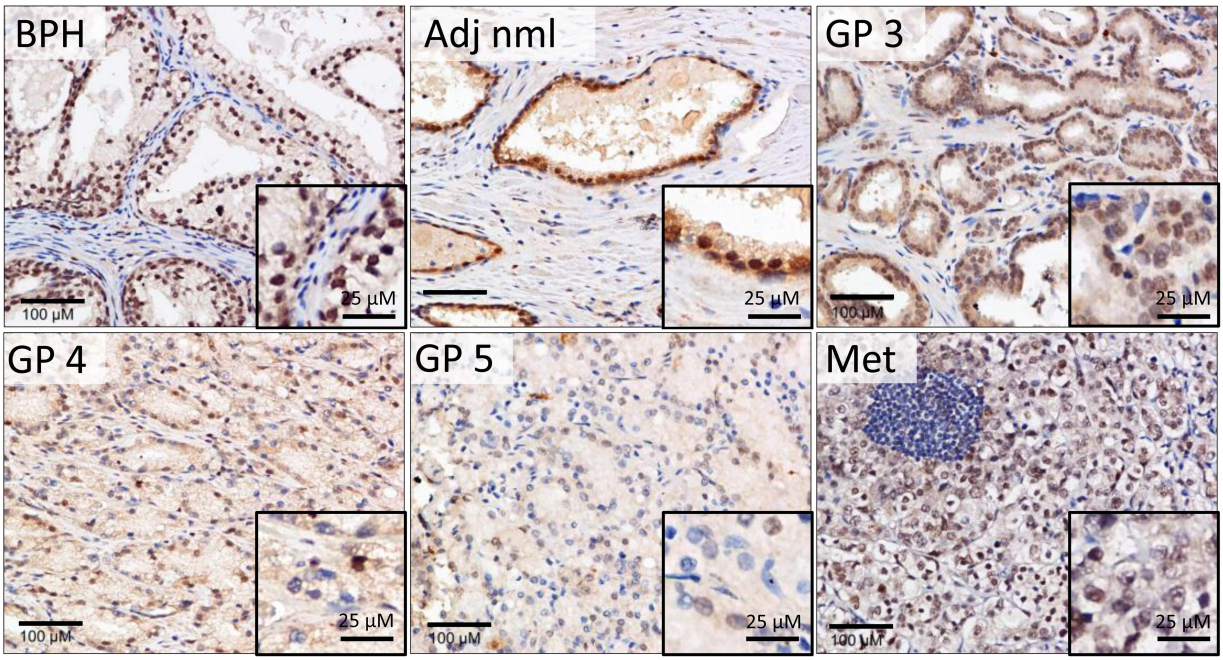

FIGURE 2 HOXA10 protein expression in human prostate. Representative images of benign prostate, localized prostate cancer and lymph node metastasis. Tissue sections were immunostained with anti-HOXA10. Scale bars represent 100 and 25 microns in low and high magnification inserts, respectively. [Color figure can be viewed at wileyonlinelibrary.com]

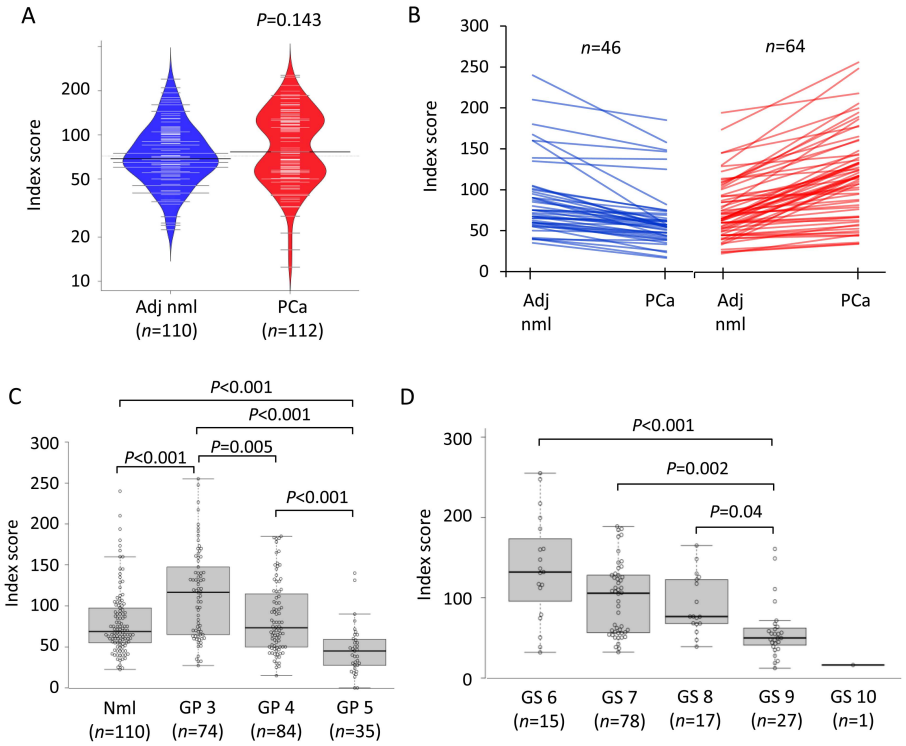

FIGURE 3 Immunohistochemical expression profile of HOXA10 in radical prostatectomy cases. (A) Beanplot comparing HOXA10 index scores in normal adjacent tissue and prostate cancer, Significance represents two-tailed Student's *t*-test. (B) Comparison of HOXA10 expression in paired normal and cancer tissues. HOXA10 index scores according to Gleason pattern (C) and Gleason score (D). Significance represent Dunn's post hoc test for individual comparisons, upon significant one way ANOVA ($P < 0.001$ for C and D). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Correlation between HOXA10 expression and clinical features

	Age	Initial PSA	Gleason pattern	Gleason score	Stage	Biochemical failure	PSA nadir after RP
Pearson correlation	0.0733	−0.104	−0.469	−0.478	−0.401	0.0045	0.0509
P-value	0.442	0.274	<0.01	<0.01	<0.01	0.962	0.594
N	112	112	112	112	112	112	112

4 | DISCUSSION

HOXA10 is a key transcription factor tasked with the regulation of prostate morphogenesis, differentiation and adult tissue homeostasis. Herein, we have shown that HOXA10 is reduced in PCa and its expression is associated with key clinicopathological features such as Gleason score/pattern, pathological stage and differentiation. Furthermore, low expression of HOXA10 was associated with shorter time to BCR. Although, IHC expression of HOXA10 was not an independent predictor of BCR, our data suggested biologically significant roles for HOXA10 and were supported by similar expression patterns in a clinically relevant mouse model of prostate cancer.

Homeobox genes have diverse biological roles in solid tumors and have been found to control a number of critical of key cellular processes such cell proliferation,[26,27] tumor angiogenesis,[28] invasion and metastasis[12,29] As a result, some homeobox genes such as *NKX3.1* also function to suppress cancers.[30] Other homeobox genes such as *HOXA 9* have shown duplicitous roles exhibiting tumor promoting effects for ovarian cancer, but showing tumor suppressing activity in breast cancer.[31,32] *HOXA10* is a homeobox gene that has also demonstrated context and cancer-specific roles. For example, HOXA10 has been shown to suppress invasion and metastasis by downregulating the expression of snail and inducing the expression of E-cadherin in endometrial carcinoma cells.[12] Additionally, breast cancer cells, overexpressing HOXA10 reduced their invasiveness through p53 regulation.[13] Elevated HOXA10 expression in gastric cancer cells was shown to inhibit proliferation and motility and its expression in gastric cancer patients was associated with a better prognosis.[14] Conversely, others have reported that HOXA10 was correlated with poor survival in patients with clear cell ovarian carcinoma[15] and promoted oral squamous cell carcinoma proliferation, migration and invasion.[33]

The biological and clinical significance of HOXA10 in PCa has not been determined. Here, we have shown that HOXA10 expression was inversely associated with tumor differentiation, a feature that is similar

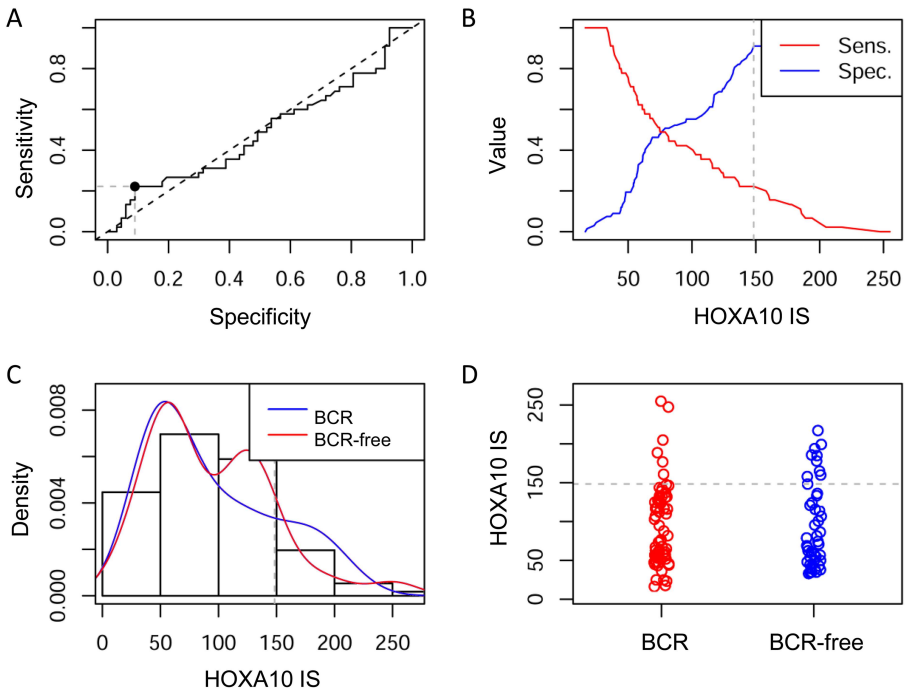

FIGURE 4 Determination of HOXA10 index sensitivity and specificity. Receiver operating characteristics (ROC) analysis was performed to determine the value of HOXA10 expression in prostate cancer as a potential biomarker and determination of an optimal HOXA10 index score cutoff. ROC (A), sensitivity and specificity (B), and histogram plots (C) of HOXA10 index score. (D) Scatterplot of individual HOXA10 index scores in biochemical recurrence (BCR) versus BCR-free cases using an optimal cutoff of 150. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Association between HOXA10 expression and clinical features

Variable		HOXA10 Index score		
		≤150 (*n* = 107)	>150 (*n* = 15)	*P*-value
Age (years)	<70	59	8	0.789
	≥70	38	7	
Initial PSA (ng/mL)	<10	56	8	0.968
	≥10	41	7	
Gleason score	≤7	54	13	0.046
	≥8	43	2	
Tumor differentiation	Well	12	7	0.002
	Moderately	42	6	
	Poor	43	2	
Stage	pT2	57	12	0.198
	pT3/4	40	3	
Biochemical recurrence	Relapse—Free	36	9	0.162
	PSA failure	61	6	
PSA nadir of after RP	<0.005	37	8	0.404
	≥0.005	60	7	

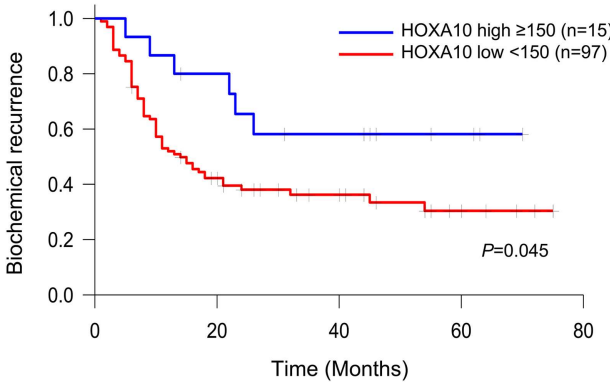

FIGURE 5 Kaplan-Meier analysis of HOXA10 expression to predict biochemical recurrence. Significance represent log-rank test. [Color figure can be viewed at wileyonlinelibrary.com]

to both gastric[14] and ovarian[12] cancers. We found no significant differences between cancer and normal adjacent tissue in matching cases. We also noted that HOXA10 expression had a Gaussian distribution in histologically normal prostate glands whereas a bimodal distribution was observed in PCa (Figure 3A). Moreover, HOXA10 expression was higher in Gleason pattern three compared to normal tissues, but the exhibited grade-dependent decrease. It is possible that normal tissues may not be truly normal[22] and could have altered HOXA10 expression or there are distinct but context-dependent roles for HOXA10 function. Aberrant and context-dependent roles other HOX genes in the development of cancers has been observed.[34]

Further evidence for possible duplicitous roles of HOXA10 is supported by the fact that a portion of high HOXA10-expressing PCa experienced longer time to BCR.

Genetic testing is becoming more and more a part of standard practice because of its potential benefits. However, there are some gaps to fill as gene testing can be limited depending on the panel and application. IHC offers a technically less challenging, cost-efficient and widely available option. From this viewpoint, IHC testing for biomarkers should be complimentary to other testing platforms and candidate biomarkers such have clear cutoffs and demonstrate good specificity. We sought to determine the possibility of HOXA10 as a potential biomarker for BCR after RP. Unfortunately, HOXA10 IHC expression profiling performed poorly with ROC analysis and failed to be a prognostic independent predictor of BCR.

While HOXA10 is an unlikely candidate for further biomarker studies in prostate cancer, its role in cancer regulation is quite apparent. Further evidence of this notion is supported by our

TABLE 4 Univariate and multivariate analyses of factors associated with biochemical recurrence after radical prostatectomy

		Univariate			Multivariate		
		OR	95%CI	*P*-value	OR	95%CI	*P*-value
Age	<70	(Reference)	0.34-1.60	0.57			
	≥70	0.74					
Initial PSA	<10	(Reference)	0.41-1.92	0.93			
	≥10	0.89					
Gleason score	≤7	(Reference)	1.93-11.13	<0.001	(Reference)	1.30-10.63	0.014
	≥8	4.65			3.73		
Stage	pT2	(Reference)	1.45-7.95	0.007	(Reference)	0.54-4.20	0.43
	pT3/pT4	3.39			1.50		
PSA nadir after RP	<0.005	(Reference)	2.97-16.14	<0.001	(Reference)	2.59-16.02	<0.001
	≥0.005	6.93			6.44		
HOXA10 index score	≥150	(Reference)	1.21-16.14	0.049	(Reference)	0.42-5.54	0.52
	<150	3.54			1.52		

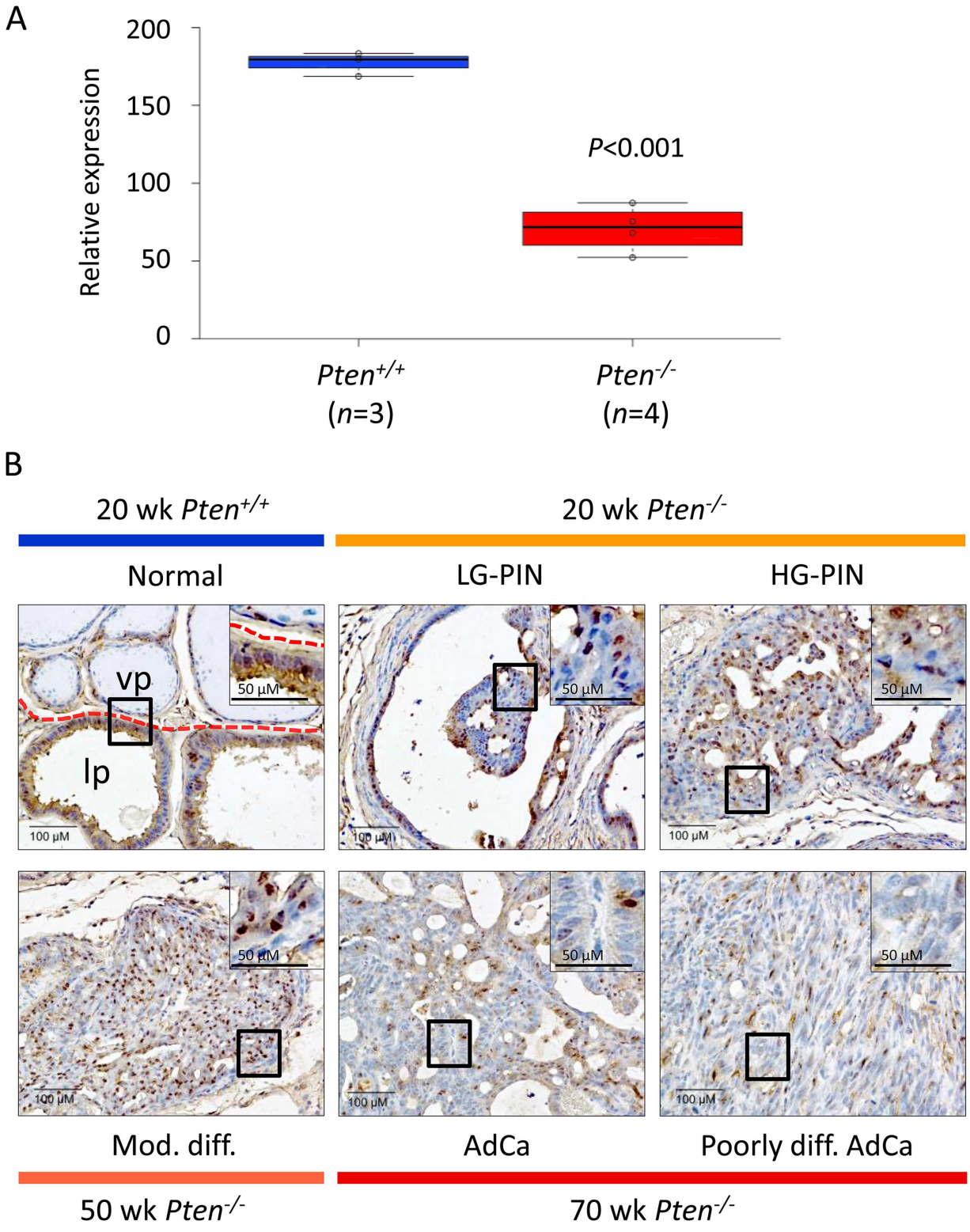

FIGURE 6 HOXA10 expression in mouse *Pten*-deficient prostate cancer. (A) Expression levels of *Hoxa10* mRNA were measured in 20-week-old prostates of wildtype and *Pten*-deficient tumor bearing mice by qRT-PCR. Significance represents two-tailed Student's *t*-test. (B) Representative images of spatial-temporal protein expression HOXA10 expression mouse *Pten*-deficient prostate tumors. [Color figure can be viewed at wileyonlinelibrary.com]

exploratory data for HOXA10 expression in a conditional transgenic mouse model of PCa. In this de novo mouse PCa model, we observed similarities between the expression patterns of HOXA10 in tumors, namely the inverse relationship between HOXA10 expression and tumor differentiation. Given the roles HOX genes in tissue differentiation and homeostasis, it not unreasonable to assume that aberrant HOX expression in tumors affects tumor development, survival and progression. This notion is reinforced by data showing *HOXB13(G84E)* germline mutations increase the risk of hereditary prostate cancer.

In summary, we have used human and mouse prostate cancer tissues to characterize HOXA10. From a clinical perspective, HOXA10 expression was inversely related to tumor differentiation and high HOXA10 expression was associated with longer times to BCR. Together our data provides evidence to link HOXA10 and PCa, however, more work is need to define the precise biological functions of HOXA10 in PCa.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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